Review Article

Vitamin D supplementations and mortality among patients with moderate/severe COVID-19: A meta-analysis of randomized controlled trials

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Background: Vitamin D deficiency is associated with severe COVID 19 and poor outcomes. However, the role of Vitamin D supplementation on mortality is controversial. The current meta analysis aimed to investigate the same among patients with COVID 19. **Materials and Methods:** We searched six databases from inception up to July 2023. The keywords used were COVID 19, SARS COV 2, mortality, Vitamin D, calcitriol, cholecalciferol, Calcifediol, survival, death, small dose, and high dose. Eight hundred and sixteen studies were retrieved, 103 full texts were screened, and 14 randomized controlled trials were included in the meta analysis. A structured checklist was used to gather the author's name, country, year of publication, Vitamin D dose, age, sex, number of patients, mortality, and comorbidities. The Cochrane system for meta analysis (RevMan, version 5.4) was used for the data analysis. **Results:** No association was found between Vitamin D supplementation and mortality among patients with COVID 19, odd ratio, 1.16, 95% confidence interval (CI), 0.84–1.59, and P = 0.36. No difference between high and low dose Vitamin D supplementation, odd ratio, 0.65, 95% CI, 0.37–1.57, and P = 0.13. In a sub analysis, no significant statistical difference was found between low dose Vitamin D supplementation versus placebo, and when considering patients who were Vitamin D deficient, odd ratio, 1.10, 95% CI, 0.74–1.63. The P = 0.64 and, odd ratio, 0.99, 95% CI, 0.71–1.40, and P = 0.97 respectively. **Conclusion:** No association was evident between Vitamin D supplementation and mortality among patients with COVID 19 irrespective of doses and Vitamin D status. Further studies are needed to address the timing and frequency of Vitamin D supplementations.

Key words: COVID-19, mortality, SARS-COV-2, Vitamin D

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INTRODUCTION

The most dramatic event of the current century is the COVID-19 pandemic. More than 617 million cases and 6.5 million death were confirmed globally until October 2022.[1] Importantly, worrisome new immune-evasive strains are discovered continuously, and one of the strains may cause a big wave, hospitalization, and mortality.[2] The challenge is the new strain with high transmission, severe presentation, and involvement of multiple organs including the heart, brain, and kidney.[3]

In the aftermath of COVID-19, a great challenge is still present due to the long-COVID or postacute COVID-19 syndrome. The persistence of symptoms (fatigue, cognitive decline among others in people who recovered is called post-COVID-19 syndrome or long COVID-19).

The prevalence of post-COVID-19 at 90 days is substantial with a great burden on the patients and health-care system.[4] Vitamin D's antimicrobial effects are well known, in addition, macrophages and T-lymphocytes can synthesize 1, 25-hydroxy Vitamin D. Therefore, the anti-inflammatory effects of Vitamin D depend on the availability of the 25-hydroxy variant.

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The anti-inflammatory effects of Vitamin D are protective against tissue damage following COVID-19 infection.[5,6]

Vitamin D neutralizes the hyper-activation of immune cells and cytokines release induced by COVID-19 (cytokines storm), cytokine storm, and inflammation strongly disturb the microvasculature and alveolar membrane in the lung, leading to alveolar edema.[7] In addition, alveolar macrophages and airway epithelium through the expression of the enzyme CYP27B1 and Vitamin D receptors enhance viral clearance and neutralization.[8] Vitamin D activates nucleotide-binding oligomerization domain-containing protein 2, β-defensin 2, and cathelicidin and suppresses hepcidin. The results are the destruction of the viral membrane, potentiate antimicrobial action, and restriction of iron by infected cells.[9]

Vitamin D and its effects on genes and immunity were shown to reduce the rate and severity of COVID-19 infection.[10,11] However, the effects of Vitamin D supplementation on the same are inconclusive.

Hosseini *et al*.,[12] D'Ecclesiis *et al*.,[13] and Szarpak *et al*.[14] pooled observational studies with minimal randomized controlled trials and found lower mortality among patients who received Vitamin D. Varikasuvu *et al*.[15] who included six randomized trials observed the same findings.

On the other hand, Rawat *et al*.,[16] Pal *et al*.,[17] and Feiner Solís *et al*.[18] conducted meta-analyses of observational and controlled trials and found no reduction of mortality among those who received Vitamin D supplementation. Importantly, Pal *et al*.[17] found that Vitamin D supplementation is effective only if given during COVID-19 infection, while supplementations before the attack were not. Feiner Solís *et al*.[18] observed the benefit of continuous Vitamin D supplementation as opposed to a single dose. The above findings raised the importance of the dose and timing of Vitamin D supplementation.

Nikniaz *et al*.[19] three randomized trials and found no benefit of Vitamin D supplementation, Shah *et al*.,[20] Tentolouris *et al*.,[21] and Beran *et al*.[22] included both observational and randomized trials and confirmed Nikniaz *et al*.[19] findings. While Kümmel *et al*.[23] included eight studies and found similar results.

More recent meta-analysis published by Zhang *et al*.[24] who included eight trials and Sîrbu *et al*.[25] who included 13 trials found no beneficial effects of Vitamin D supplementation on mortality. The above studies were limited by pooling both observational and randomized trials and included only small-randomized controlled trials. Therefore, an update regarding this important topic is needed. Therefore, the current study aimed to assess Vitamin D supplementation's effects on mortality among patients with COVID-19 patients.

MATERIALS AND METHODS

Eligibility criteria according to PICOS.

Inclusion criteria

Studies were included if they were randomized controlled trials assessing the association between COVID-19 mortality and Vitamin D supplementation.

Exclusion criteria

Retrospective studies, prospective cohorts, case-control, cross-sectional studies, systematic reviews, and meta-analyses were not included. Experts' opinions, editorials, case reports, series, and protocols without data were excluded from the study. Studies conducted among children and those that focus on prevention were not included.

Outcome measures

- The outcome measures were the effects of low-dose versus high-dose Vitamin D supplementations on mortality among patients with COVID-19
- The effects of Vitamin D supplementations versus placebo on mortality among patients with COVID-19.

Secondary outcomes

- The effects of Vitamin D supplementation on mortality among Vitamin D deficient patients with COVID-19
- To compare low doses of Vitamin D supplementation versus placebo effects on mortality.

In the present meta-analysis, we did not specify the route of administration of Vitamin D supplementations. Both Vitamin D deficient and those with normal Vitamin D levels were included.

Literature search: Two authors independently searched six databases (Web of Science, SCOPUS, PubMed, MEDLINE, Google Scholar, Cochrane Library, and EBSCO). The literature search was conducted during July 2023 and the studies were included without time limitation (from inception up to the recently published article). The keywords used were (we used both MeSH Terms and all fields) COVID-19, SAR-COV-2, mortality, Vitamin D, calcitriol, cholecalciferol, Calcifediol, survival, death, small dose, and high dose. Eight hundred and sixteen studies were retrieved, and 703 remained after duplication removal, of them 103 full texts were screened. However, only 14 randomized controlled trials were included in the final meta-analysis [Figure 1].

Data extraction

A structured checklist was used to gather the author's name, country, year of publication, Vitamin D dose, and the results. The age of patients with COVID-19, sex, number of patients and mortality, and comorbidities at baseline was also reported Tables 1-3.

Risk of bias assessment

We used the Oob-2 risk of the bias assessment tool, the two authors independently assessed the trials regarding seven domains, two for selection, and one for performance, detection, attrition, reporting, and overall bias.[26] Five studies showed some concern, and nine studies were of low risk of bias.

Statistical analysis

RevMan, version, 5.4 (the most recent version of the Cochrane system, Cochrane organisation Headquarters, London, England) was used to analyze the dichotomous data of 15 cohorts from 14 randomized controlled trials.

Table 1: Mortality among patients with COVID-19 on high- and low-dose Vitamin D supplementation

Author	Country	Low dose	High dose	Age/years	Sex/females	Vitamin D dose	Adverse events	Results (*P*)
Annweiler *et al*., 2022	France	14/127	8/127	89 versus 87	65% versus 52%	50,000 IU versus 200,000	34.6% versus 42.9%	Significant (0.049)
Sabico *et al*., 2021	Saudi Arabia	1/36	0/33	53.5±12.3 versus 46.3±15.2	60.6% versus 41.7%	1000 versus 5000 IU	No adverse events in both arms	Not significant (0.39)
Serhan *et al*., 2022	Egypt	30/58	26/58	65.7±12.6 versus 66.1±11.2	20.7% versus 34.5%	Alfacalcidol 1 μg/day versus 200,000 IU	Not assessed	Not significant (0.45)

Table 2: Age, sex, Vitamin D dose, and comorbidities among patients with COVID-19 on Vitamin D supplementation and placebo

Author	Country	Vitamin D	Placebo	Age/years	Sex/ females	Vitamin D dose	Comorbidities	Results (*P*)
Annweiler *et al*., 2022	France	6/45	10/32	87.7±5.4 versus 88.6±5.7	56.7% versus 28.6%	50,000 IU per month, or 80,000 IU 100,000 IU, or 200,000 IU every 2–3 months	Controls had more malignancy	Significant (0.03)
Bychinin *et al*., 2022	Russia	19/52	27/54	65.4 versus 63.5	58% versus 43	60,000 IU/weekly followed by daily 5000 IU	No differences regarding comorbidities	Not significant (0.16)
Cannata-Andía *et al*., 2022	Spain	22/274	15/269	59 versus 57	33.9% versus 36.1%	100,000 IU of cholecalciferol once	No differences regarding comorbidities	Not significant (0.205)
Domazet Bugarin *et al*., 2023	Croatia	23/75	27/77	65 versus 65.5	30.7% versus 25%	10,000 IU daily	Intervention groups had more malignancy	Not significant (0.56)
Elamir *et al*., 2022	USA	0/25	3/25	69±18 versus 64±16	52% versus 48%	Calcitriol 0.5 μg daily for 14 days or hospital discharge	No differences regarding comorbidities	Significant (0.23)
Entrenas Castillo *et al*., 2020	Spain	1/50	2/26	53.14±10.77 versus 52.77±9.35	46% versus 31%	Oral calcifediol 0.532 mg, day 1, then 0.266 mg on days 3 and 7, and then weekly	Patients on Vitamin D had more diabetes and hypertension	Significant (0.03)
Maghbooli *et al*., 2021	Iran	5/53	6/53	50±15 versus 49±13	22% versus 20%	30 capsules of calcifediol twice (30,000–60,000)	No differences regarding comorbidities	Not significant (0.7)
Mariani *et al*., 2022	Argentina	5/115	2/103	59.8±10.7 versus 58.3±10.6	44.3% versus 50.5%	500,000 IU	More cancer in the interventional group	Not Significant (0.541)
Murai *et al*., 2021	Brazil	9/119	6/118	56.5±13.8 versus 56±15.0	41.2% versus 46.6%	A single oral dose of 200,000 IU	Diabetes commoner among the intervention group	Not significant (0.41)
Rastogi *et al*., 2022	India	0/16	0/24	50 versus 47.5	62.5% versus 50%	Daily 60,000 IU	Patients with comorbidities were excluded	Not significant (>0.05)
Sánchez-Zuno *et al*., 2021	Mexico	0/20	0/22	44 versus 43	31.8% versus 30%	10,000 IU of Vitamin D3 for 14 days	No differences regarding comorbidities	Not significant (>0.05)
Soliman *et al*., 2021	Egypt	7/40	3/16	71.30±4.16 versus 70.19±4.57	Not reported	200,000 IU intramuscularly	No differences regarding comorbidities	Not significant (0.83)

Table 3: Risk of bias assessment of the included studies according to the Cochrane risk of bias of randomized controlled trials (risk of bias-2)

Author	Selection bias[a]	Selection bias[b]	Performance bias	Attrition bias	Detection bias	Reporting bias	Overall bias
Mariani *et al*., 2022	Low	Low	Low	Some concern	Some concern	Some concern	Low
Annweiler *et al*., 2022	Some concern	Some concern	Low	Low	Low	Low	Low
Bychinin *et al*., 2022	Low	Some concern	Some concerns	Some concern	Some concerns	Low	Some concerns
Entrenas Castillo *et al*., 2020	Low	Low	Low	Some concerns	Low	Low	Low
Maghbooli *et al*., 2021	Low	Low	Low	Low	Low	Low	Low
Domazet Bugarin *et al*., 2023	Low	Low	Some concerns	Low	Low	Some concerns	Low
Cannata-Andía *et al*., 2022	Low	Low	Some concerns	Low	Low	Low	Low
Elamir *et al*., 2022	Low	Low	Low	Some concerns	Some concerns	Some concerns	Some concerns
Murai *et al*., 2021	Low	Low	Low	Low	Low	Low	Low
Rastogi *et al*., 2022	Some concerns	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
Sánchez-Zuno *et al*., 2021	Some concerns	Some concerns	Some concerns	Low	Low	Low	Some concerns
Soliman *et al*., 2021	Low	Low	Low	Low	Some concerns	Some concerns	Low
Serhan *et al*., 2022	Low	Low	Low	Some concerns	Low	Some concerns	Low
Sabico *et al*., 2021	Some concerns	Some concerns	Some concerns	Low	Low	Low	Some concerns

[a]Random sequence generation, [b]Allocation concealment

Three studies assessed the low dose versus high-dose Vitamin D supplementation and 12 cohorts assessed low dose versus placebo. The data were entered manually and the fixed effect was used (because of the nonsignificant heterogeneity). To assess the association between Vitamin D supplementation and mortality, we adopted the odd ratio with 95% confidence interval (CI) for the dichotomous data. Sensitivity analysis was conducted after the exclusion of studies with high or uncertain risk of bias. Two comparisons were conducted to assess the effects of Vitamin D supplementation and placebo and high versus low-dose Vitamin D supplementation. In addition, two sub-analysis assessed the effects of low-dose Vitamin D supplementation and placebo and Vitamin D deficient patients. $P < 0.05$ was considered statistically significant [Figures 2-5].

RESULTS

Characteristics of the included trials

The study included 15 cohorts from 14 randomized controlled trials.[11,27-39] Twelve cohorts assessed Vitamin D supplementation versus placebo with 1703 patients and 198 mortality. While three cohorts compared low-dose versus high-dose Vitamin D supplementations. Five studies were from Europe, four from Asia, two from Africa, three from South America, and one from the USA. The age of the patients ranged from 43 years to 88.6 ± 5.7 years. Some of the studies were not matched for sex; Vitamin D varied greatly from 1000 IUs to 200,000 IUs with different routes with some studies using Calcitriol. Comorbidities substantially differ between intervention and control groups. In this meta-analysis, participants in nine of the included studies were either Vitamin D deficient or insufficient; two were conducted among patients with sufficient Vitamin D levels, while Vitamin D levels were not mentioned in three trials.

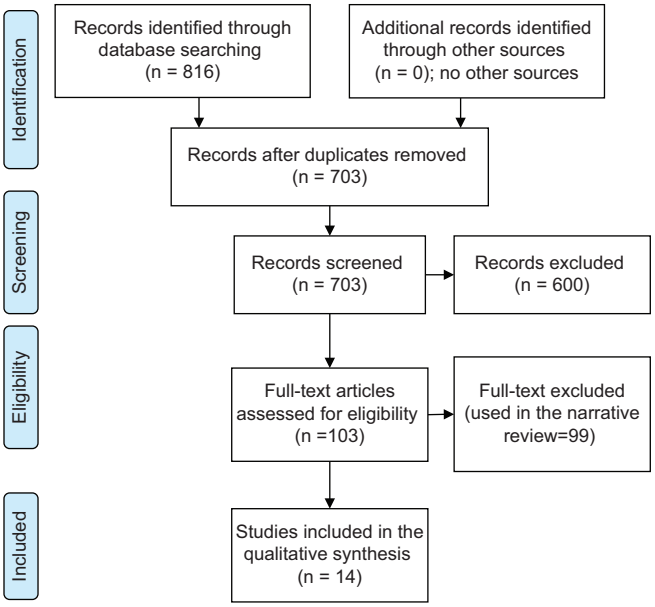

Figure 1: Randomized controlled studies assessed the effects of low/high dose Vitamin D supplementation on COVID-19 mortality (the PRISMA chart)

In the present meta-analysis, no association was found between Vitamin D and mortality among patients with COVID-19, odd ratio, 1.16, 95% CI, O.84–1.59, the *P* value for overall effect was 0.36, the Chi-square, 11.1, and the degree of freedom = 9. There was no significant heterogeneity, I^2 for heterogeneity, 19%, and $P = 0.27$ [Figure 2].

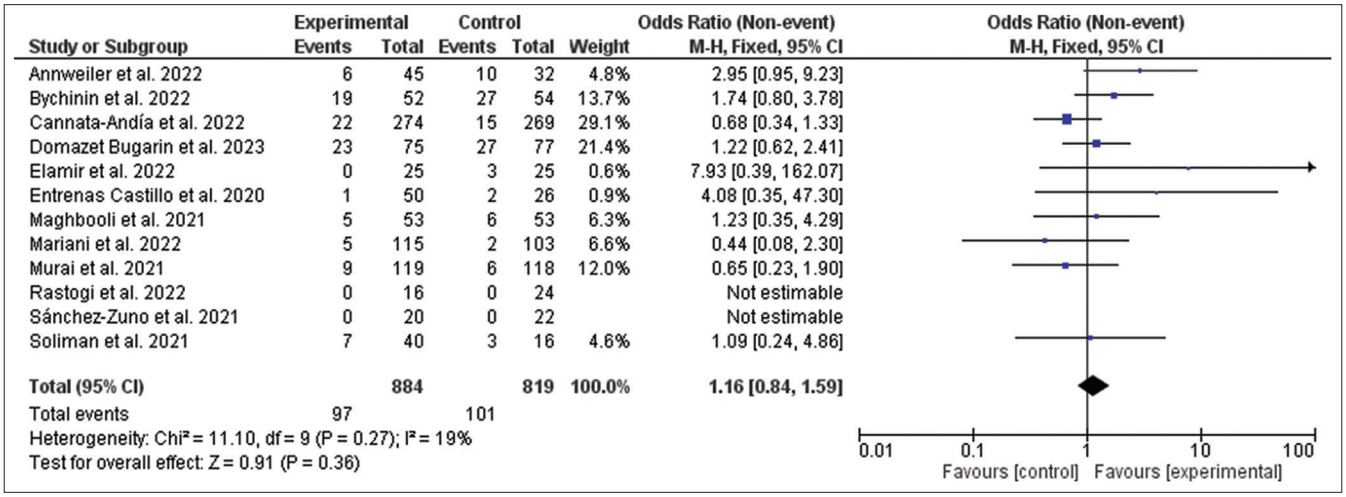

Figure 2: Mortality among patients with COVID-19 on Vitamin D supplementation and placebo. CI: Confidence interval

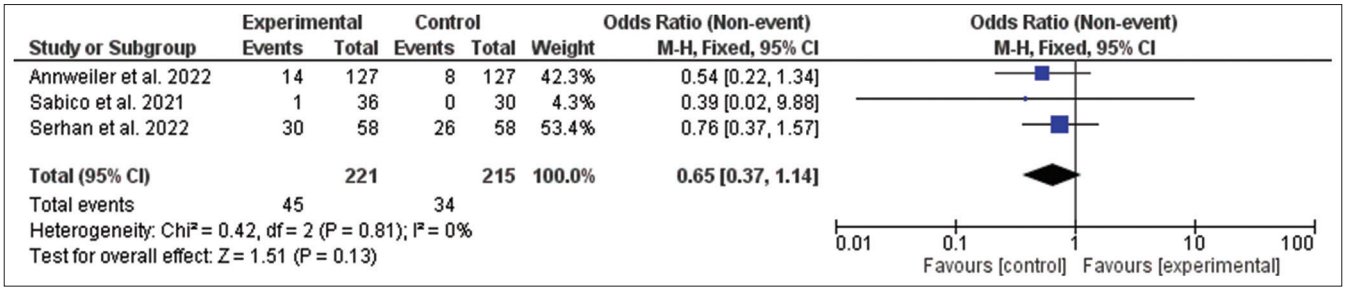

Figure 3: Mortality among patients with COVID-19 on high- and low-dose Vitamin D supplementation. CI: Confidence interval

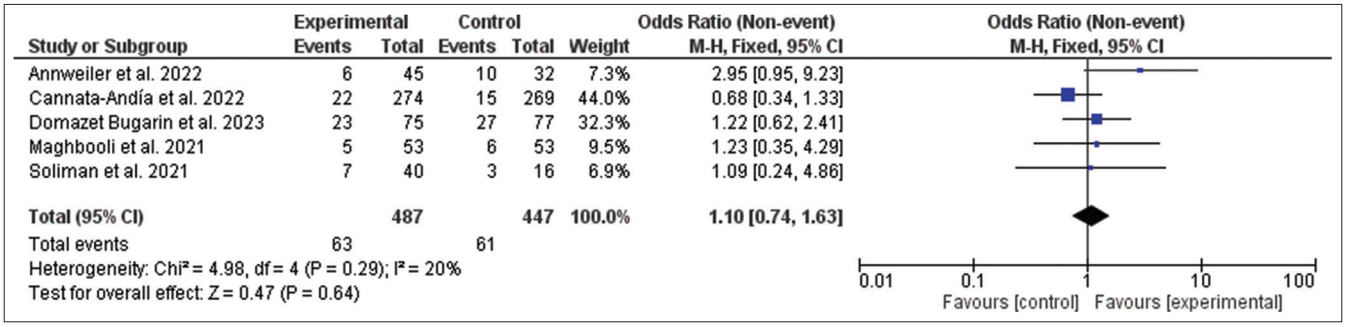

Figure 4: Mortality among patients with COVID-19 on Vitamin low-dose D supplementation and placebo. CI: Confidence interval

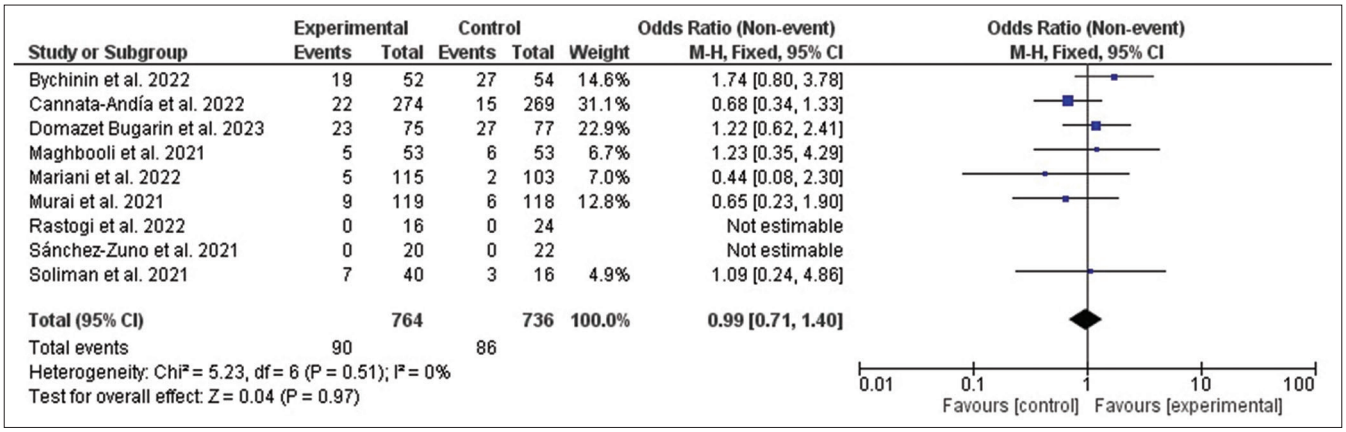

Figure 5: Mortality among Vitamin D deficient patients with COVID-19 on Vitamin D supplementation. CI: Confidence interval

Regarding Vitamin D dose, no significant statistical was found between high- and low-dose Vitamin D supplementation, odd ratio, 0.65, 95% CI, O.37–1.57, the *P* value for overall effect was 0.13, the Chi-square, 0.42, and the degree of freedom = 2. There was no significant heterogeneity, I^2 for heterogeneity, 0%, and *P* = 0.81 [Figure 3].

In a sub-analysis, no significant statistical difference was found between low-dose Vitamin D supplementation versus placebo, odd ratio, 1.10, 95% CI, O.74–1.63. The *P* value for the overall effect was 0.64, the Chi-square was 4.98, and the degree of freedom = 4 was. There was no significant heterogeneity, I^2 for heterogeneity, 20%, and *P* = 0.29 [Figure 4].

Regarding the effect of Vitamin D therapy among patients who were Vitamin D deficient, nine trials were included with 1500 patients.[11,30,31,34-39] No significant effect was found, odd ratio, 0.99, 95% CI, 0.71–1.40, and *P* value for overall effect, 0.97. No heterogeneity was observed, $I^2 = 0.0$ and *P* value for heterogeneity, 0.51 [Figure 5].

DISCUSSION

In the present meta-analysis, no association was found between Vitamin D supplementation and mortality among patients with COVID-19, odd ratio, 1.16, 95% CI, O.84–1.59. No differences were evident between high- and low-dose supplementation, odd ratio, 0.65, 95% CI, O.37–1.57. In addition, no benefit of low-dose Vitamin D supplementation compared to placebo (odd ratio, 1.10, 95% CI, O.74–1.63) and when Vitamin D was administered to patients with Vitamin D deficiency at baseline, odd ratio, 0.99, 95% CI, 0.71–1.40.

Although Vitamin D deficiency is associated with severe COVID-19 deficiency and poor outcomes, Vitamin D supplementation's effects on mortality are controversial.[40] The current findings were in contradiction to previous meta-analyses.[12-19,41]

Hosseini *et al*.[12] included five studies (only one randomized trial) and found a protective effect of Vitamin D supplementation on COVID-19 mortality. Importantly, mortality was not assessed as the primary outcome.

A meta-analysis published by D'Ecclesiis *et al*.[13] confirmed the same. However, they included only four randomized controlled trials. Further studies conducted by Szarpak *et al*.,[14] Varikasuvu *et al*.,[15] and Rawat *et al*.[16] included eight, six, and three trials, respectively, and found a reduction in mortality. Pal *et al*.[17] pooled 13 studies with only three trials and confirmed the above findings only when Vitamin D was administered post-COVID-19 diagnosis. Importantly, Pal *et al*. pooled mortality with intensive care admission as a single outcome.

Feiner Solís *et al*.[41] included the largest studies (eleven) and concluded the benefit of Vitamin D supplementation on mortality regardless of Vitamin D status. However, the positive effects were only observed if sustained administration of Vitamin D was adopted. Although the authors also assessed the levels of Vitamin D level postsupplementation, however, they included studies published by the same authors, in addition to the heterogeneity across the included studies. All the above meta-analyses confirmed the findings of Nikniaz *et al*.[19] who published a meta-analysis with a limited number of patients and study number.

The current findings are in line with previous meta-analyses that found no significant effects on mortality among COVID-19 patients on Vitamin D supplementations.[20-25] A meta-analysis conducted by Shah *et al*.[20] observed no benefit of Vitamin D supplementation on mortality, but the heterogeneity and the fact that only two randomized trials were included limited their results. Tentolouris *et al*.[21] included nine studies and found no benefit of Vitamin D supplementation, but the substantial heterogeneity limited their conclusion. Beran *et al*.[22] pooled observational (nine studies) and randomized controlled trials (four) and found no effect of Vitamin D supplementation, the substantial heterogeneity (77%) and the small number of randomized trials limited their findings. The authors found no effects when Vitamin D is taken before or after post-COVID-19 diagnosis. Kümmel *et al*.[23] observed similar findings with significant heterogeneity. There are two recent meta-analyses, which assessed mortality and found no benefit of Vitamin D supplementation in this regard. Zhang *et al*.[24] included both observational and randomized trials (only eight). The authors found no effects of supplementation regardless of Vitamin D status or doses. Sîrbu *et al*.[25] included 13 trials. However, only eight trials were on mortality and the authors included studies published among both adults and pediatrics. In addition, the study focused on high-dose Vitamin D supplementation. Furthermore, the moderate heterogeneity limited their findings.

The lack of Vitamin D supplementation effects might be related to the late time of the introduction in the presence of severe inflammation resulting in impaired metabolism.[42] In addition, a single dose of 200000 IUs of Vitamin D might enhance the metabolism of Vitamin D3 to the inactive 25-hydroxyvitamin.[43] Importantly, a single high dose of Vitamin D may result in intracellular Vitamin D deficiency despite the apparent normal serum

concentration; high intermittent doses delay the activation of 1, 25-hydroxy Vitamin D and increase the inactive 24, 25-hydroxyl vitamin variant.[44] Therefore, a single dose of Vitamin D is not enough to increase the antimicrobial proteins, including regulatory T-cells, cathelicidin, and defensins.[45,46]

In the present study, the majority of the included studies used intermittent or single high-dose. Therefore, the effects might be different if the high dose is administered before the COVID-19 attack to ensure better antimicrobial and anti-inflammatory effects. The issue of Vitamin D level at the time of supplementation is not expected to add any benefit because Vitamin D is strongly bound to albumin and Vitamin D binding protein. Therefore, its level is expected to be low during infection.[47,48] The important issues when considering Vitamin D administration are the dose and time of administration, a cumulative dose of <200000 IUs is considered a low dose, and the daily recommended dose is 10,000/day.[17] A single bolus dose of 100000 IUs is recommended by the Spanish Agency for Medicines and Health to avoid hyperkalcemia and achieve optimal levels in a few days.[46,49]

The strength of this meta-analysis is that we included the largest up-to-date randomized trials with a low risk of bias; we assessed high versus low dose Vitamin D supplementation, and the effects of Vitamin D supplementation on patients who were Vitamin D deficient at baseline. In addition, demographic data and the baseline comorbidities were reported. Our results can inform the scientific community due to the absence or low heterogeneity across the trials included.

Limitations

The study has several limitations: Some of the included studies were placebo-controlled, while others used no placebo or blinding. The dose and route of Vitamin D varies significantly across the included studies. The patient's characteristics and comorbidities vary significantly, and the virus strain might differ. Furthermore, the patients' quality of care was not uniform. The included studies did not compare the important risk factors including the time before COVID-19 onset and Vitamin D supplementations. In addition, socioeconomic level and other nutrients including Vitamin C were not addressed.

CONCLUSION

Vitamin D supplementation among patients with moderate-to-severe COVID-19 was not associated with mortality reduction in low dose, single high dose, or intermittent administration. No significant effects on mortality were evident when comparing high and low doses and low dose supplementation against placebo. The results remained robot even after assessing the effects of Vitamin D supplementation among patients who were Vitamin D deficient. Further studies assessing the effects of Vitamin D supplementations and controlling for socioeconomic characteristics, the time lag between the onset of COVID-19 and supplementation, and the quality of care are needed.

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Conflicts of interest

There are no conflicts of interest.

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